

PHARMACEUTICAL COMPOSITIONS BASED ON ANTICHOLINERGICS AND  
PDE-IV INHIBITORS

RELATED APPLICATIONS

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Benefit of U.S. Provisional Application Serial No. 60/407,895, filed on September 3, 2002 is hereby claimed, and said application is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

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The present invention relates to novel pharmaceutical compositions based on new anticholinergics and PDE-IV inhibitors, processes for preparing them and their use in the treatment of respiratory diseases.

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BRIEF DESCRIPTION OF THE DRAWING

Figure 1 depicts a particularly preferred inhaler for administering the pharmaceutical composition according to the present invention.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel pharmaceutical compositions based on anticholinergics and PDE-IV inhibitors, processes for preparing them and their use in the treatment of respiratory diseases.

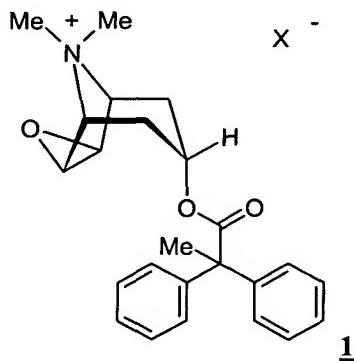
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Surprisingly, an unexpectedly beneficial therapeutic effect, particularly a synergistic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if one or more, preferably one, anticholinergic of formula 1 is used with one or more, preferably one, PDE-IV inhibitor 2. In view of this synergistic effect the pharmaceutical combinations according to the invention can be used in smaller doses than would be the case with the individual compounds used in monotherapy in the usual way.

Furthermore, this reduces unwanted side effects such as may occur when PDE-IV inhibitors are administered, for example.

The effects mentioned above may be observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are  
5 administered successively in separate formulations. According to the invention, it is preferable to administer the two active substance ingredients simultaneously in a single formulation.

Within the scope of the present invention the anticholinergics used are the salts of formula  
**1**



10

wherein

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X - denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate.

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Preferably, the salts of formula **1** are used wherein

X - denotes an anion with a single negative charge selected from the group consisting of chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide.

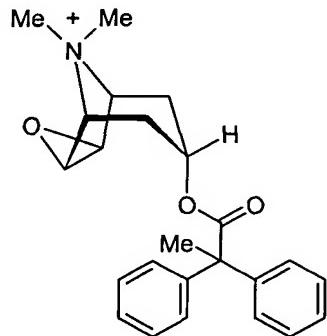
Most preferably, the salts of formula 1 are used wherein

X - denotes an anion with a single negative charge selected from the group consisting of chloride, bromide and methanesulphonate, preferably bromide.

- 5 Particularly preferred according to the invention is the salt of formula 1 wherein  
X - denotes bromide.

The salts of formula 1 are known from International Patent Application WO 02/32899.

- 10 Within the scope of the present patent application, an explicit reference to the pharmacologically active cation of formula

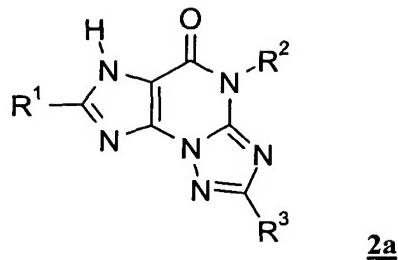


can be recognised by the use of the designation 1'. Any reference to compounds 1 naturally includes a reference to the cation 1'.

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Any reference within the scope of the present invention to the salts 1 which may be used according to the invention includes any hydrates and solvates of these compounds which may optionally be obtained.

- 20 Within the scope of the present invention, the preferred PDE-IV inhibitors (2) are compounds selected from among enprofylline, theophylline, roflumilast, ariflo (cilomilast), Bay-198004, CP-325,366, BY343, D-4396 (Sch-351591), V-11294A, AWD-12-281, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide and the tricyclic nitrogen heterocycles of general formula 2a



wherein

- 5       $R^1$       denotes  $C_1$ - $C_5$ -alkyl,  $C_5$ - $C_6$ -cycloalkyl, phenyl, benzyl or a 5- or 6-membered, saturated or unsaturated heterocyclic ring which may contain one or two heteroatoms selected from among oxygen and nitrogen;
- 10      $R^2$       denotes  $C_1$ - $C_5$ -alkyl or  $C_2$ - $C_4$ -alkenyl;
- 15      $R^3$       denotes  $C_1$ - $C_5$ -alkyl which may optionally be substituted by  $C_1$ - $C_4$ -alkoxy,  $C_5$ - $C_6$ -cycloalkyl, phenoxy or a 5- or 6-membered, saturated or unsaturated heterocyclic ring which may contain one or two heteroatoms selected from among oxygen and nitrogen;  $C_5$ - $C_6$ -cycloalkyl or phenyl or benzyl optionally substituted by  $C_1$ - $C_4$ -alkoxy,
- 20     wherein the compounds of formula **2a** are optionally in the form of their racemates, their enantiomers, in the form of the diastereomers and the mixtures thereof, optionally in the form of their tautomers and optionally the pharmacologically acceptable acid addition salts thereof.

Of the abovementioned compounds of formula **2a** those which are preferably used within the scope of the present invention are those compounds of formula **2a** wherein

- 1       $R^1$       denotes  $C_1$ - $C_4$ -alkyl,  $C_5$ - $C_6$ -cycloalkyl, tetrahydrofuryl, tetrahydropyranyl, piperazinyl, morpholinyl or phenyl;
- 2       $R^2$       denotes  $C_1$ - $C_4$ -alkyl or  $C_2$ - $C_4$ -alkenyl;

$R^3$  denotes C<sub>1</sub>-C<sub>4</sub>-alkyl which may optionally be substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>5</sub>-C<sub>6</sub>-cycloalkyl, phenoxy, (C<sub>1</sub>-C<sub>4</sub>-alkoxy)phenyloxy, piperazine or pyrrole, C<sub>5</sub>-C<sub>6</sub>-cycloalkyl or phenyl or benzyl optionally substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy,

5 optionally in the form of their racemates, their enantiomers, in the form of the diastereomers and the mixtures thereof, optionally in the form of their tautomers and optionally the pharmacologically acceptable acid addition salts thereof.

10 Of the compounds of formula **2a** those which are most preferably used within the scope of  
the present invention are those compounds of formula **2a** wherein

$R^1$  denotes ethyl, propyl, butyl, cyclopentyl, tetrahydrofuryl, tetrahydropyrranyl, N-morpholinyl or phenyl;

$R^2$  denotes ethyl, propyl, allyl or butenyl;

15 R<sup>3</sup> denotes ethyl, propyl, butyl, cyclopentyl, cyclohexylmethyl, benzyl,  
phenylethyl, phenoxyethyl, methoxybenzyl or N-pyrrolylmethyl,  
optionally in the form of their racemates, their enantiomers, in the form of the  
diastereomers and the mixtures thereof, optionally in the form of their  
tautomers and optionally the pharmacologically acceptable acid addition salts  
thereof.  
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Most preferably, the compounds used as component 2 are the compounds of formula 2a  
wherein

R<sup>1</sup> denotes ethyl, n-propyl, tert-butyl, cyclopentyl, 3-tetrahydrofuryl, N-morpholinyl or phenyl;  
 25  
 R<sup>2</sup> denotes ethyl or n-propyl;  
 R<sup>3</sup> denotes ethyl, i-propyl, n-propyl, n-butyl, t-butyl, cyclopentyl, cyclohexylmethyl, benzyl, phenylethyl, phenoxyethyl, 4-methoxybenzyl or N-pyrrollylmethyl, optionally in the form of their racemates, their  
 30 enantiomers, in the form of the diastereomers and the mixtures thereof,

optionally in the form of their tautomers and optionally the pharmacologically acceptable acid addition salts thereof.

- Examples of alkyl groups (including those which are part of other groups) are branched and unbranched alkyl groups with 1 to 5 carbon atoms, such as, for example: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec. butyl, tert.butyl, n-pentyl, isopentyl or neopentyl. The abbreviations Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, etc. may optionally be used for the abovementioned groups.
- 10 Examples of cycloalkyl groups with 5 or 6 carbon atoms include cyclopentyl or cyclohexyl. Examples of 5- or 6-membered, saturated or unsaturated heterocyclic rings which may contain one or two heteroatoms selected from among oxygen and nitrogen include: furan, tetrahydrofuran, tetrahydrofuranone,  $\gamma$ -butyrolactone,  $\alpha$ -pyran,  $\gamma$ -pyran, dioxolan, tetrahydropyran, dioxan, pyrrole, pyrroline, pyrrolidine, pyrazole, pyrazoline, 15 imidazole, imidazoline, imidazolidine, pyridine, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, morpholine, oxazole, isoxazole, oxazine and pyrazolidine.

Table 1 lists the compounds of general formula 2a which are most preferably used in conjunction with the compounds 1 within the scope of the invention.

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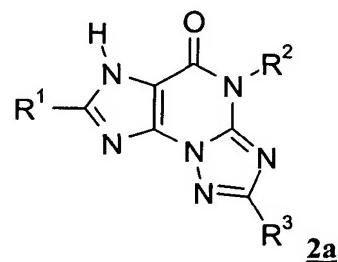


Table 1:

No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
1	cyclopentyl	n-propyl	i-propyl

No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
2	cyclopentyl	n-propyl	ethyl
3	t-butyl	ethyl	4-methoxybenzyl
4	cyclopentyl	ethyl	-CH <sub>2</sub> CH <sub>2</sub> phenyl
5	3-tetrahydrofuryl	ethyl	benzyl
6	cyclopentyl	n-propyl	n-propyl
7	t-butyl	ethyl	benzyl
8	phenyl	n-propyl	n-propyl
9	cyclopentyl	ethyl	benzyl
10	-n-propyl	-n-propyl	benzyl
11	cyclopentyl	ethyl	N-pyrrolylmethyl
12	cyclopentyl	-n-propyl	benzyl
13	cyclopentyl	-n-propyl	-t-butyl
14	cyclopentyl	n-propyl	n-butyl
15	cyclopentyl	ethyl	-CH <sub>2</sub> -O-phenyl
16	N-morpholinyl	-n-propyl	benzyl
17	cyclopentyl	ethyl	cyclohexylmethyl
18	ethyl	ethyl	cyclohexylmethyl
19	n-propyl	n-propyl	cyclopentyl

The compounds of general formula 2a may be prepared analogously to the method described in the prior art for certain of the above-defined compounds of general formula (I) (Tenor et al., *Chem. Ber.* Vol. 97 (1964) p. 1373-1382), to which reference is hereby made.

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Preferably, also, the compound 2 is selected from among enprofylline, roflumilast, ariflo, AWD-12-281 and N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-

cyclopropylmethoxybenzamide, while ariflo, roflumilast, AWD-12-281 and the abovementioned compounds of formula 2a are particularly preferred as compound 2 according to the invention.

- 5 Any reference to the abovementioned PDE-IV inhibitors 2 within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts thereof which may exist.

- By the physiologically acceptable acid addition salts which may be formed from 2 are meant, according to the invention, pharmaceutically acceptable salts selected from the salts  
10 of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Particularly preferred salts of the compounds 2 according to the invention are those selected from among the acetate, hydrochloride, hydrobromide, sulphate, phosphate and methanesulphonate.
- 15 The pharmaceutical combinations of 1 and 2 according to the invention are preferably administered by inhalation. Suitable inhalable powders packed into suitable capsules (inhalettes) may be administered using suitable powder inhalers. Alternatively, the drug may be inhaled by the application of suitable inhalation aerosols. These also include inhalation aerosols which contain HFA134a (also known as TG134a), HFA227 (also  
20 known as TG227) or a mixture thereof as propellant gas. The drug may also be inhaled using suitable solutions of the pharmaceutical combination consisting of 1 and 2.

In one aspect, therefore, the invention relates to a pharmaceutical composition which contains a combination of 1 and 2.

- 25 In another aspect the present invention relates to a pharmaceutical composition which contains one or more salts 1 and one or more compounds 2, optionally in the form of their solvates or hydrates. Again, the active substances may be combined in a single preparation

or contained in two separate formulations. Pharmaceutical compositions which contain the active substances 1 and 2 in a single preparation are preferred according to the invention.

In another aspect the present invention relates to a pharmaceutical composition which contains, in addition to therapeutically effective quantities of 1 and 2, a pharmaceutically acceptable excipient. In another aspect the present invention relates to a pharmaceutical composition which does not contain any pharmaceutically acceptable excipient in addition to therapeutically effective quantities of 1 and 2.

The present invention also relates to the use of 1 and 2 for preparing a pharmaceutical composition containing therapeutically effective quantities of 1 and 2 for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD), and complications thereof such as pulmonary hypertension, as well as allergic and non-allergic rhinitis.

The present invention also relates to the simultaneous or successive use of therapeutically effective doses of the combination of the above pharmaceutical compositions 1 and 2 for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD), and complications thereof such as pulmonary hypertension, as well as allergic and non-allergic rhinitis, by simultaneous or successive administration.

In the active substance combinations of 1 and 2 according to the invention, ingredients 1 and 2 may be present in the form of their enantiomers, mixtures of enantiomers or in the form of racemates.

The proportions in which the two active substances 1 and 2 may be used in the active substance combinations according to the invention are variable. Active substances 1 and 2 may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds 1 and 2, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various compounds and their different potencies. As a rule, the pharmaceutical combinations

according to the invention may contain compounds 1 and 2 in ratios by weight ranging from 1:100 to 100:1, preferably from 1:80 to 80:1. In particularly preferred pharmaceutical combinations, the weight ratios of 1 to 2 are most preferably in a range in which 1' and 2 are present in proportions of 1:50 to 50:1, more preferably from 1:20 to 5 20:1.

For example, without restricting the scope of the invention thereto, preferred combinations of 1' and PDE-IV inhibitor 2 may contain [*error in the German text*] in the following weight ratios:

1:65; 1:64; 1:63; 1:62; 1:61; 1:60; 1:59; 1:58; 1:57; 1:56; 1:55; 1:54; 1:53; 1:52; 1:51; 1:50; 10 1:49; 1:48; 1:47; 1:46; 1:45; 1:44; 1:43; 1:42; 1:41; 1:40; 1:39; 1:38; 1:37; 1:36; 1:35; 1:34; 1:33; 1:32; 1:31; 1:30; 1:29; 1:28; 1:27; 1:26; 1:25; 1:24; 1:23; 1:22; 1:21; 1:20; 1:19; 1:18; 1:17; 1:16; 1:15; 1:14; 1:13; 1:12; 1:11; 1:10; 1:9; 1:8; 1:7; 1:6; 1:5; 1:4; 1:3; 1:2; 1:1; 2:1; 3:1; 4:1; 5:1; 6:1; 7:1; 8:1; 9:1; 10:1; 11:1; 12:1; 13:1; 14:1; 15:1; 16:1; 17:1; 18:1; 19:1; 20:1.

15 The pharmaceutical compositions according to the invention containing the combinations of 1 and 2 are normally administered so that 1 and 2 are present together in doses of 0.01 to 10000 $\mu$ g, preferably from 0.1 to 2000 $\mu$ g, more preferably from 1 to 1500 $\mu$ g, better still from 50 to 1200 $\mu$ g per single dose. For example, combinations of 1 and 2 according to the invention contain a quantity of tiotropium 1' and PDE-IV inhibitor 2 such that the total 20 dosage per single dose is about 100 $\mu$ g, 105 $\mu$ g, 110 $\mu$ g, 115 $\mu$ g, 120 $\mu$ g, 125 $\mu$ g, 130 $\mu$ g, 135 $\mu$ g, 140 $\mu$ g, 145 $\mu$ g, 150 $\mu$ g, 155 $\mu$ g, 160 $\mu$ g, 165 $\mu$ g, 170 $\mu$ g, 175 $\mu$ g, 180 $\mu$ g, 185 $\mu$ g, 190 $\mu$ g, 195 $\mu$ g, 200 $\mu$ g, 205 $\mu$ g, 210 $\mu$ g, 215 $\mu$ g, 220 $\mu$ g, 225 $\mu$ g, 230 $\mu$ g, 235 $\mu$ g, 240 $\mu$ g, 245 $\mu$ g, 250 $\mu$ g, 255 $\mu$ g, 260 $\mu$ g, 265 $\mu$ g, 270 $\mu$ g, 275 $\mu$ g, 280 $\mu$ g, 285 $\mu$ g, 290 $\mu$ g, 295 $\mu$ g, 300 $\mu$ g, 305 $\mu$ g, 310 $\mu$ g, 315 $\mu$ g, 320 $\mu$ g, 325 $\mu$ g, 330 $\mu$ g, 335 $\mu$ g, 340 $\mu$ g, 345 $\mu$ g, 350 $\mu$ g, 25 355 $\mu$ g, 360 $\mu$ g, 365 $\mu$ g, 370 $\mu$ g, 375 $\mu$ g, 380 $\mu$ g, 385 $\mu$ g, 390 $\mu$ g, 395 $\mu$ g, 400 $\mu$ g, 405 $\mu$ g, 410 $\mu$ g, 415 $\mu$ g, 420 $\mu$ g, 425 $\mu$ g, 430 $\mu$ g, 435 $\mu$ g, 440 $\mu$ g, 445 $\mu$ g, 450 $\mu$ g, 455 $\mu$ g, 460 $\mu$ g, 465 $\mu$ g, 470 $\mu$ g, 475 $\mu$ g, 480 $\mu$ g, 485 $\mu$ g, 490 $\mu$ g, 495 $\mu$ g, 500 $\mu$ g, 505 $\mu$ g, 510 $\mu$ g, 515 $\mu$ g, 520 $\mu$ g, 525 $\mu$ g, 530 $\mu$ g, 535 $\mu$ g, 540 $\mu$ g, 545 $\mu$ g, 550 $\mu$ g, 555 $\mu$ g, 560 $\mu$ g, 565 $\mu$ g, 570 $\mu$ g,

575μg, 580μg, 585μg, 590μg, 595μg, 600μg, 605μg, 610μg, 615μg, 620μg, 625μg,  
 630μg, 635μg, 640μg, 645μg, 650μg, 655μg, 660μg, 665μg, 670μg, 675μg, 680μg,  
 685μg, 690μg, 695μg, 700μg, 705μg, 710μg, 715μg, 720μg, 725μg, 730μg, 735μg,  
 740μg, 745μg, 750μg, 755μg, 760μg, 765μg, 770μg, 775μg, 780μg, 785μg, 790μg,  
 5 795μg, 800μg, 805μg, 810μg, 815μg, 820μg, 825μg, 830μg, 835μg, 840μg, 845μg,  
 850μg, 855μg, 860μg, 865μg, 870μg, 875μg, 880μg, 885μg, 890μg, 895μg, 900μg,  
 905μg, 910μg, 915μg, 920μg, 925μg, 930μg, 935μg, 940μg, 945μg, 950μg, 955μg,  
 960μg, 965μg, 970μg, 975μg, 980μg, 985μg, 990μg, 995μg, 1000μg, 1005μg, 1010μg,  
 10 1015μg, 1020μg, 1025μg, 1030μg, 1035μg, 1040μg, 1045μg, 1050μg, 1055μg, 1060μg,  
 15 1065μg, 1070μg, 1075μg, 1080μg, 1085μg, 1090μg, 1095μg, 1100μg or similar. The  
 suggested dosages per single dose specified above are not to be regarded as being limited  
 to the numerical values actually stated, but are intended as dosages which are disclosed by  
 way of example. Of course, dosages which may fluctuate about the abovementioned  
 numerical values within a range of about +/- 2.5 μg are also included in the values given  
 above by way of example. In these dosage ranges, the active substances 1' and 2 may be  
 present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations of 1  
 and 2 according to the invention may contain a quantity of 1' and PDE-IV inhibitor 2 such  
 that, for each single dose, 16.5μg of 1' and 25μg of 2, 16.5μg of 1' and 50μg of 2,  
 20 16.5μg of 1' and 100μg of 2, 16.5μg of 1' and 200μg of 2, 16.5μg of 1' and 300μg of  
2, 16.5μg of 1' and 400μg of 2, 16.5μg of 1' and 500μg of 2, 16.5μg of 1' and 600μg of  
2, 16.5μg of 1' and 700μg of 2, 16.5μg of 1' and 800μg of 2, 16.5μg of 1' and 900μg of  
2, 16.5μg of 1' and 1000μg of 2, 33.1μg of 1' and 25μg of 2, 33.1μg of 1' and 50μg of  
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 25 2, 33.1μg of 1' and 400μg of 2, 33.1μg of 1' and 500μg of 2, 33.1μg of 1' and 600μg of  
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If the active substance combination in which 1 denotes the bromide is used as the preferred combination of 1 and 2 according to the invention, the quantities of active substance 1' and 2 administered per single dose mentioned by way of example correspond to the following quantities of 1 and 2 administered per single dose: 20 $\mu$ g of 1 and 25 $\mu$ g of 2, 20 $\mu$ g of 1 and 50 $\mu$ g of 2, 20 $\mu$ g of 1 and 100 $\mu$ g of 2, 20 $\mu$ g of 1 and 200 $\mu$ g of 2, 20 $\mu$ g of 1 and 300 $\mu$ g of 2, 20 $\mu$ g of 1 and 400 $\mu$ g of 2, 20 $\mu$ g of 1 and 500 $\mu$ g of 2, 20 $\mu$ g of 1 and 600 $\mu$ g of 2, 20 $\mu$ g of 1 and 700 $\mu$ g of 2, 20 $\mu$ g of 1 and 800 $\mu$ g of 2, 20 $\mu$ g of 1 and 900 $\mu$ g of 2, 20 $\mu$ g of 1 and 1000 $\mu$ g of 2, 40 $\mu$ g of 1 and 25 $\mu$ g of 2, 40 $\mu$ g of 1 and 50 $\mu$ g of 2, 40 $\mu$ g of 1 and 100 $\mu$ g of 2, 40 $\mu$ g of 1 and 200 $\mu$ g of 2, 40 $\mu$ g of 1 and 300 $\mu$ g of 2, 40 $\mu$ g of 1 and 400 $\mu$ g of 2, 40 $\mu$ g of 1 and 500 $\mu$ g of 2, 40 $\mu$ g of 1 and 600 $\mu$ g of 2, 40 $\mu$ g of 1 and 700 $\mu$ g of 2, 40 $\mu$ g of 1 and 800 $\mu$ g of 2, 40 $\mu$ g of 1 and 900 $\mu$ g of 2, 40 $\mu$ g of 1 and 1000 $\mu$ g of 2, 60 $\mu$ g of 1 and 25 $\mu$ g of 2, 60 $\mu$ g of 1

of 1 and 50 $\mu$ g of 2, 60 $\mu$ g of 1 and 100 $\mu$ g of 2, 60 $\mu$ g of 1 and 200 $\mu$ g of 2, 60 $\mu$ g of 1 and 300 $\mu$ g of 2, 60 $\mu$ g of 1 and 400 $\mu$ g of 2, 60 $\mu$ g of 1 and 500 $\mu$ g of 2, 60 $\mu$ g of 1 and 600 $\mu$ g of 2, 60 $\mu$ g of 1 and 700 $\mu$ g of 2, 60 $\mu$ g of 1 and 800 $\mu$ g of 2, 60 $\mu$ g of 1 and 900 $\mu$ g of 2, 60 $\mu$ g of 1 and 1000 $\mu$ g of 2, 100 $\mu$ g of 1 and 25 $\mu$ g of 2, 100 $\mu$ g of 1 and 50 $\mu$ g of 2, 100 $\mu$ g of 1 and  
5 100 $\mu$ g of 2, 100 $\mu$ g of 1 and 200 $\mu$ g of 2, 100 $\mu$ g of 1 and 300 $\mu$ g of 2, 100 $\mu$ g of 1 and 400 $\mu$ g  
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10 1 and 200 $\mu$ g of 2, 200 $\mu$ g of 1 and 300 $\mu$ g of 2, 200 $\mu$ g of 1 and 400 $\mu$ g of 2, 200 $\mu$ g of 1 and  
500 $\mu$ g of 2, 200 $\mu$ g of 1 and 600 $\mu$ g of 2, 200 $\mu$ g of 1 and 700 $\mu$ g of 2, 200 $\mu$ g of 1 and 800 $\mu$ g  
of 2, 200 $\mu$ g of 1 and 900 $\mu$ g of 2, 200 $\mu$ g of 1 and 1000 $\mu$ g of 2, 250 $\mu$ g of 1 and 25 $\mu$ g of 2,  
250 $\mu$ g of 1 and 50 $\mu$ g of 2, 250 $\mu$ g of 1 and 100 $\mu$ g of 2, 250 $\mu$ g of 1 and 200 $\mu$ g of 2, 250 $\mu$ g  
of 1 and 300 $\mu$ g of 2, 250 $\mu$ g of 1 and 400 $\mu$ g of 2, 250 $\mu$ g of 1 and 500 $\mu$ g of 2, 250 $\mu$ g of 1  
and 600 $\mu$ g of 2, 250 $\mu$ g of 1 and 700 $\mu$ g of 2, 250 $\mu$ g of 1 and 800 $\mu$ g of 2, 250 $\mu$ g of 1 and  
15 900 $\mu$ g of 2, 250 $\mu$ g of 1 and 1000 $\mu$ g of 2, 500 $\mu$ g of 1 and 25 $\mu$ g of 2, 500 $\mu$ g of 1 and 50 $\mu$ g  
of 2, 500 $\mu$ g of 1 and 100 $\mu$ g of 2, 500 $\mu$ g of 1 and 200 $\mu$ g of 2, 500 $\mu$ g of 1 and 300 $\mu$ g of 2,  
500 $\mu$ g of 1 and 400 $\mu$ g of 2, 500 $\mu$ g of 1 and 500 $\mu$ g of 2, 500 $\mu$ g of 1 and 600 $\mu$ g of 2, 500 $\mu$ g  
of 1 and 700 $\mu$ g of 2, 500 $\mu$ g of 1 and 800 $\mu$ g of 2, 500 $\mu$ g of 1 and 900 $\mu$ g of 2 or 500 $\mu$ g of 1  
and 1000 $\mu$ g of 2.

20

The active substance combinations of 1 and 2 according to the invention are preferably administered by inhalation. For this purpose, ingredients 1 and 2 have to be made available in forms suitable for inhalation. Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions. Inhalable powders according to the invention containing the combination of active substances 1 and 2 may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The preparations according to the invention may contain the combination of active substances 1 and 2 either together in one  
25  
30

formulation or in two separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

**A) Inhalable powder containing the combinations of active substances 1 and 2**

5 **according to the invention:**

The inhalable powders according to the invention may contain 1 and 2 either on their own or in admixture with suitable physiologically acceptable excipients.

If the active substances 1 and 2 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare

10 these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is  
15 preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to 250 $\mu\text{m}$ , preferably between 10 and 150 $\mu\text{m}$ , most

20 preferably between 15 and 80 $\mu\text{m}$ . It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9 $\mu\text{m}$  to the excipients mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance 1 and 2, preferably with an average particle size of 0.5 to  
25 10 $\mu\text{m}$ , more preferably from 1 to 5 $\mu\text{m}$ , is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and by finally mixing the ingredients together are known from the prior art. The inhalable powders according to the invention may be prepared and administered either in the form of

a single powder mixture which contains both 1 and 2 or in the form of separate inhalable powders which contain only 1 or 2.

The inhalable powders according to the invention may be administered using inhalers known from the prior art. Inhalable powders according to the invention which contain a physiologically acceptable excipient in addition to 1 and 2 may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630A, or by other means as described in DE 36 25 685 A. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to 1 and 2 are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

A particularly preferred inhaler for using the pharmaceutical combination according to the invention in inhalettes is shown in Figure 1.

This inhaler (Handyhaler) for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured via a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, and a mouthpiece 12 which is connected to the housing 1, the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut, and air through-flow holes 13 for adjusting the flow resistance.

If the inhalable powders according to the invention are packed into capsules (inhalettes) for the preferred use described above, the quantities packed into each capsule should be 1 to 30mg, preferably 3 to 20mg, more particularly 5 to 10mg of inhalable powder per capsule. These capsules contain, according to the invention, either together or separately, the doses of 1' and 2 mentioned hereinbefore for each single dose.

**B) Propellant gas-driven inhalation aerosols containing the combinations of active substances 1 and 2:**

Inhalation aerosols containing propellant gas according to the invention may contain substances 1 and 2 dissolved in the propellant gas or in dispersed form. 1 and 2 may be present in separate formulations or in a single preparation, in which 1 and 2 are either both dissolved, both dispersed or only one component is dissolved and the other is dispersed.

- 5 The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof.
- 10 Particularly preferred propellant gases are halogenated alkane derivatives selected from TG134a, TG227 and mixtures thereof.

The propellant-driven inhalation aerosols according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

- 15 The inhalation aerosols containing propellant gas according to the invention may contain up to 5 wt.-% of active substance 1 and/or 2. Aerosols according to the invention contain, for example, 0.002 to 5 wt.-%, 0.01 to 3 wt.-%, 0.015 to 2 wt.-%, 0.1 to 2 wt.-%, 0.5 to 2 wt.-% or 0.5 to 1 wt.-% of active substance 1 and/or 2.

- 20 If the active substances 1 and/or 2 are present in dispersed form, the particles of active substance preferably have an average particle size of up to 10 $\mu\text{m}$ , preferably from 0.1 to 5 $\mu\text{m}$ , more preferably from 1 to 5 $\mu\text{m}$ .

The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers).

- 25 Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of propellant-driven aerosols as hereinbefore described combined with one or more inhalers suitable for administering these aerosols. In addition, the present invention relates to inhalers which are characterised in that they contain the propellant gas-

containing aerosols described above according to the invention. The present invention also relates to cartridges which are fitted with a suitable valve and can be used in a suitable inhaler and which contain one of the above-mentioned propellant gas-containing inhalation aerosols according to the invention. Suitable cartridges and methods of filling these  
5 cartridges with the inhalable aerosols containing propellant gas according to the invention are known from the prior art.

**C) Propellant-free inhalable solutions or suspensions containing the combinations of active substances 1 and 2 according to the invention:**

It is particularly preferred to use the active substance combination according to the  
10 invention in the form of propellant-free inhalable solutions and suspensions. The solvent used may be an aqueous or alcoholic, preferably an ethanolic solution. The solvent may be water on its own or a mixture of water and ethanol. The relative proportion of ethanol compared with water is not limited but the maximum is up to 70 percent by volume, more particularly up to 60 percent by volume and most preferably up to 30 percent by volume.  
15 The remainder of the volume is made up of water. The solutions or suspensions containing 1 and 2, separately or together, are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of  
20 particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred.  
25 If desired, mixtures of the above acids may be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

According to the invention, the addition of editic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabiliser or complexing agent is unnecessary in the present formulation. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium edetate is less than 100mg/100ml,  
5 preferably less than 50mg/100 ml, more preferably less than 20mg/100 ml. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10mg/100ml are preferred.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions according to the invention. Preferred co-solvents are those which contain hydroxyl groups  
10 or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycoether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in  
15 the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates,  
20 polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

The preferred excipients include antioxidants such as ascorbic acid, for example, provided  
25 that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins occurring in the human body.

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium

chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50mg/100ml, more preferably between 5 and 20mg/100ml.

- 5 Preferred formulations contain, in addition to the solvent water and the combination of active substances 1 and 2, only benzalkonium chloride and sodium edetate. In another preferred embodiment, no sodium edetate is present.

The propellant-free inhalable solutions according to the invention are administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Within the scope of the present invention, preferred inhalers are those in which a quantity of less than 100 $\mu$ L, preferably less than 50 $\mu$ L, more preferably between 20 and 30 $\mu$ L of active substance solution can be nebulised in 10 preferably one spray action to form an aerosol with an average particle size of less than 15 20 $\mu$ m, preferably less than 10 $\mu$ m, in such a way that the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

An apparatus of this kind for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687 (cf. in particular Figures 6a and 6b). 20 The nebulisers (devices) described therein are known by the name Respimat®.

This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols according to the invention containing the combination of active substances 1 and 2. Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide, this device can be carried at all times by the patient. The nebuliser sprays a defined 25 volume of pharmaceutical formulation using high pressures through small nozzles so as to produce inhalable aerosols.

The preferred atomiser essentially consists of an upper housing part, a pump housing, a nozzle, a locking mechanism, a spring housing, a spring and a storage container, characterised by

- a pump housing which is secured in the upper housing part and which comprises at 5 one end a nozzle body with the nozzle or nozzle arrangement,
- a hollow plunger with valve body,
- a power takeoff flange in which the hollow plunger is secured and which is located in the upper housing part,
- a locking mechanism situated in the upper housing part,
- 10 - a spring housing with the spring contained therein, which is rotatably mounted on the upper housing part by means of a rotary bearing,
- a lower housing part which is fitted onto the spring housing in the axial direction.

The hollow plunger with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is axially movable within the cylinder. Reference is made in particular to Figures 1 to 4, especially Figure 3, and the relevant parts of the description. The hollow plunger with valve body exerts a pressure of 15 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the fluid, the measured amount of active substance solution, at its high pressure end at the moment when the spring is actuated. Volumes of 10 to 50 microlitres are preferred, while 20 volumes of 10 to 20 microlitres are particularly preferred and a volume of 15 microlitres per spray is most particularly preferred.

The valve body is preferably mounted at the end of the hollow plunger facing the nozzle body.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by 25 microtechnology. Microstructured nozzle bodies are disclosed for example in WO-94/07607; reference is hereby made to the contents of this specification, particularly Figure 1 therein and the associated description.

The nozzle body consists for example of two sheets of glass and/or silicon firmly joined together, at least one of which has one or more microstructured channels which connect the nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth 5 preferably being 4.5 to 6.5 microns while the length is preferably 7 to 9 microns.

- In the case of a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may extend parallel to one another or may be inclined relative to one another in the direction of the nozzle opening. In a nozzle body with at least two nozzle openings at the outlet end the directions of spraying may be at an angle of 10 20 to 160° to one another, preferably 60 to 150°, most preferably 80 to 100°. The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, most preferably 30 to 70 microns. Spacings of 50 microns are most preferred. The directions of spraying will therefore meet in the vicinity of the nozzle openings.
- 15 The liquid pharmaceutical preparation strikes the nozzle body with an entry pressure of up to 600 bar, preferably 200 to 300 bar, and is atomised into an inhalable aerosol through the nozzle openings. The preferred particle or droplet sizes of the aerosol are up to 20 microns, preferably 3 to 10 microns.

The locking mechanism contains a spring, preferably a cylindrical helical compression 20 spring, as a store for the mechanical energy. The spring acts on the power takeoff flange as an actuating member the movement of which is determined by the position of a locking member. The travel of the power takeoff flange is precisely limited by an upper and lower stop. The spring is preferably biased, via a power step-up gear, e.g. a helical thrust gear, by an external torque which is produced when the upper housing part is rotated counter to 25 the spring housing in the lower housing part. In this case, the upper housing part and the power takeoff flange have a single or multiple V-shaped gear.

The locking member with engaging locking surfaces is arranged in a ring around the power takeoff flange. It consists, for example, of a ring of plastic or metal which is inherently radially elastically deformable. The ring is arranged in a plane at right angles to the atomiser axis. After the biasing of the spring, the locking surfaces of the locking member

5 move into the path of the power takeoff flange and prevent the spring from relaxing. The locking member is actuated by means of a button. The actuating button is connected or coupled to the locking member. In order to actuate the locking mechanism, the actuating button is moved parallel to the annular plane, preferably into the atomiser; this causes the deformable ring to deform in the annular plane. Details of the construction of the locking

10 mechanism are given in WO 97/20590.

The lower housing part is pushed axially over the spring housing and covers the mounting, the drive of the spindle and the storage container for the fluid.

When the atomiser is actuated the upper housing part is rotated relative to the lower housing part, the lower housing part taking the spring housing with it. The spring is

15 thereby compressed and biased by means of the helical thrust gear and the locking mechanism engages automatically. The angle of rotation is preferably a whole-number fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is biased, the power takeoff member in the upper housing part is moved along by a given distance, the hollow plunger is withdrawn inside the cylinder in the pump housing, as a result of which

20 some of the fluid is sucked out of the storage container and into the high pressure chamber in front of the nozzle.

If desired, a number of exchangeable storage containers which contain the fluid to be atomised may be pushed into the atomiser one after another and used in succession. The storage container contains the aqueous aerosol preparation according to the invention.

25 The atomising process is initiated by pressing gently on the actuating button. As a result, the locking mechanism opens up the path for the power takeoff member. The biased

spring pushes the plunger into the cylinder of the pump housing. The fluid leaves the nozzle of the atomiser in atomised form.

Further details of construction are disclosed in PCT Applications WO 97/12683 and WO 97/20590, to which reference is hereby made.

- 5 The components of the atomiser (nebuliser) are made of a material which is suitable for its purpose. The housing of the atomiser and, if its operation permits, other parts as well, are preferably made of plastics, e.g. by injection moulding. For medicinal purposes, physiologically safe materials are used.

- 10 Figures 6a/b of WO 97/12687 show the nebuliser (Respimat®) which can advantageously be used for inhaling the aqueous aerosol preparations according to the invention.

Figure 6a of WO 97/12687 to which explicit reference is hereby made shows a longitudinal section through the atomiser with the spring biased. Figure 6b of WO 97/12687 to which explicit reference is hereby made shows a longitudinal section through the atomiser with the spring relaxed. The upper housing part (51) contains the pump housing (52) on the end 15 of which is mounted the holder (53) for the atomiser nozzle. In the holder is the nozzle body (54) and a filter (55). The hollow plunger (57) fixed in the power takeoff flange (56) of the locking mechanism projects partially into the cylinder of the pump housing. At its end the hollow plunger carries the valve body (58). The hollow plunger is sealed off by means of the seal (59). Inside the upper housing part is the stop (60) on which the power 20 takeoff flange abuts when the spring is relaxed. On the power takeoff flange is the stop (61) on which the power takeoff flange abuts when the spring is biased. After the biasing of the spring the locking member (62) moves between the stop (61) and a support (63) in the upper housing part. The actuating button (64) is connected to the locking member. The upper housing part ends in the mouthpiece (65) and is sealed off by means of the 25 protective cover (66) which can be placed thereon.

The spring housing (67) with compression spring (68) is rotatably mounted on the upper housing part by means of the snap-in lugs (69) and rotary bearing. The lower housing part

(70) is pushed over the spring housing. Inside the spring housing is the exchangeable storage container (71) for the fluid (72) which is to be atomised. The storage container is sealed off by the stopper (73) through which the hollow plunger projects into the storage container and is immersed at its end in the fluid (supply of active substance solution).

- 5 The spindle (74) for the mechanical counter is mounted in the covering of the spring housing. At the end of the spindle facing the upper housing part is the drive pinion (75). The slider (76) sits on the spindle.

The nebuliser described above is suitable for nebulising the aerosol preparations according to the invention to produce an aerosol suitable for inhalation.

- 10 If the formulation according to the invention is nebulised using the method described above (Respimat®) the quantity delivered should correspond to a defined quantity with a tolerance of not more than 25%, preferably 20% of this amount in at least 97%, preferably at least 98% of all operations of the inhaler (spray actuations). Preferably, between 5 and 30 mg of formulation, most preferably between 5 and 20 mg of formulation are delivered
- 15 as a defined mass on each actuation.

However, the formulation according to the invention may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers.

- Accordingly, in a further aspect, the invention relates to pharmaceutical formulations in the form of propellant-free inhalable solutions or suspensions as described above combined
- 20 with a device suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, the invention relates to propellant-free inhalable solutions or suspensions characterised by the combination of active substances 1 and 2 according to the invention in conjunction with the device known by the name Respimat®. In addition, the present invention relates to the above-mentioned devices for inhalation, preferably the
  - 25 Respimat®, characterised in that they contain the propellant-free inhalable solutions or suspensions according to the invention as described hereinbefore.

The propellant-free inhalable solutions or suspensions according to the invention may take the form of concentrates or sterile inhalable solutions or suspensions ready for use, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®.

Formulations ready for use may be produced from the concentrates, for example, by the

5 addition of isotonic saline solutions. Sterile formulations ready for use may be administered using energy-operated fixed or portable nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

Accordingly, in another aspect, the present invention relates to pharmaceutical

10 compositions in the form of propellant-free inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile formulations ready for use, combined with a device suitable for administering these solutions, characterised in that the device is an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other

15 methods.

The Examples which follow serve to illustrate the present invention in more detail without restricting the scope of the invention to the following embodiments by way of example.

### Examples of Formulations

#### A) Inhalable powders:

20

1)

Ingredients	µg per capsule
1'- bromide	200
AWD-12-281	200
Lactose	4778.3
<b>Total</b>	<b>25000</b>

2)

Ingredients	µg per capsule
<u>1'</u> - bromide	100
compound of formula <u>2a</u>	125
Lactose	12350
<b>Total</b>	12500

3)

Ingredients	µg per capsule
<u>1'</u> - bromide	200
ariflo	250
Lactose	12250
<b>Total</b>	12500

5

4)

Ingredients	µg per capsule
<u>1'</u> - bromide	200
roflumilast	200
Lactose	24600
<b>Total</b>	25000

10 5)

Ingredients	µg per capsule
<u>1'</u> - bromide	100
roflumilast	250
Lactose	12150
<b>Total</b>	125000

6)

Ingredients	µg per capsule
<u>1'</u> - bromide	200
roflumilast	50
Lactose	12250
<b>Total</b>	12500

**B) Propellant gas-containing aerosols for inhalation:**

5

1) Suspension aerosol:

Ingredients	wt.-%
<u>1'</u> - bromide	0.020
AWD-12-281	0.060
Soya lecithin	0.2
TG 134a: TG227 = 2:3	ad 100

10 2) Suspension aerosol:

Ingredients	wt.-%
<u>1'</u> - bromide	0.039
ariflo	0.033
TG 134a	ad 100